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In situ conversion of a Ru metathesis catalyst to an isomerization catalyst†

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Addition of alcohols and substoichiometric amounts of a base to a metathesis reaction induces conversion of the metathesis-active carbene catalyst to an isomerization-active hydride species.

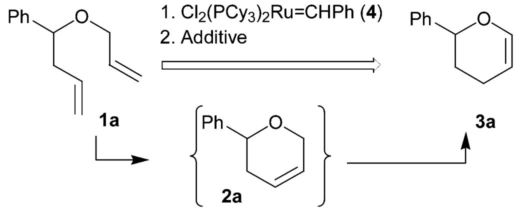
The fact that the nature of the reactive functional group is not altered in the course of an olefin metathesis reaction makes this transformation ideally suited for the construction of catalyzed reaction sequences.[1] For instance, cascades consisting of ring-opening, ring-closing and cross-metathesis steps have been found to be extremely useful in target molecule synthesis.[2a,b] The individual steps of these reaction sequences are mediated by the same catalytically active metal carbene species. Sequences that combine a metathesis step and a subsequent non-metathesis functionalization[2c] of the C–C double bond are conceptually different. These require either the use of two different compatible catalysts[3] or the selective conversion of the metal carbene catalyst to a different catalytically active species after completion of the metathesis reaction. An example of the latter class of reactions is the metathesis–hydrogenation sequence, where the C–C double bond formed in the metathesis step is subsequently hydrogenated by exchanging the inert gas atmosphere for hydrogen.[4] More recently, a metathesis–isomerization sequence has been independently developed by Snapper *et al.*[5a] and ourselves (Scheme 1).[5b] The synthetic value of this sequence is very high, as it makes cyclic enol ethers such as **3a** conveniently available from allyl homoallyl ether **1a** without isolation of the primary metathesis product **2a**. Snapper *et al.* achieved the conversion of the metathesis catalyst to an isomerization catalyst by applying a dilute hydrogen atmosphere,[5a] while our method involves the addition of substoichiometric amounts of inorganic hydrides (*e.g.* NaH, $NaBH_4$).[5b]

Metathesis–hydrogenation as well as metathesis–isomerization sequences seem to rely on the conversion of a (metathesis-active) ruthenium carbene to a (hydrogenation-/isomerization-active) ruthenium hydride[6] species *in situ*.[7,8] The development of novel methods for the *in situ* formation of ruthenium hydrides from ruthenium carbenes may therefore lead to a significant improvement in these synthetically valuable reaction sequences. Furthermore, alternative methods for *in situ* generation of Ru hydride from Ru carbene species might open up the pathway to the development of novel metathesis–non-metathesis sequences that rely on Ru hydrides as catalysts.

Recently, Louie and Grubbs reported that the Fischer-type ruthenium carbene complex $[Cl_2(PCy_3)_2Ru{=}CHOEt]$ (**5**) decomposes to the hydride complex $[Cl(CO)(PCy_3)_2Ru{-}H]$ (**6**) upon heating.[9] We planned to exploit this observation by testing ethyl vinyl ether as an additive in the ring-closing metathesis–isomerization sequence. Thus, ring-closing methathesis of **1a** was conducted in the presence of 5 mol% of **4** in toluene at ambient temperature. After complete conversion of **1a** to the primary metathesis product **2a** (TLC), a sample of the reaction mixture was analyzed by ^{31}P-NMR spectroscopy. A small amount of carbene complex **4** could still be detected [$\delta(^{31}P)$ 36.6 ppm],[10] the major part of **4** was converted to $[Cl_2(PCy_3)_2Ru{=}CH_2]$ (**7**), which was identified by its $\delta(^{31}P)$ value of 43.9 ppm.[10] Upon addition of ethyl vinyl ether (30 equiv.), the signal at 43.9 ppm rapidly disappeared and a new signal at $\delta(^{31}P)$ 37.0 ppm appeared, which is in good agreement with the literature value reported for **5**.[9] The mixture was subsequently heated to reflux to induce decomposition of **5** to the hydride complex **6**. Compound **6** is indeed formed (as indicated by a ^{31}P resonance at 47.7 ppm);[9] however, less than 10% of the primary metathesis product **2a** was isomerized to **3a** after 6 h. It may be concluded that **6** is probably not an efficient isomerization catalyst under these conditions and for the substrates in question. Nevertheless, we investigated an alternative method for the generation of **6** *in situ* that was inspired by a study recently published by Dinger and Mol.[11] These authors reported that ruthenium carbene complex **4** reacts with primary alcohols in the presence of a base to yield the same Ru hydride complex obtained by Louie and Grubbs *via* thermolysis of **5**. In a typical experiment, ethanol was added as a co-solvent after completion of the metathesis reaction, followed by 50 mol% of solid NaOH. After 4 h at 110 °C, a 1 : 1 mixture of **2a** and the desired isomerization product **3a** was obtained. Upon heating in the presence of the additives for 3 h, a ^{31}P-NMR resonance at 53.5 ppm was observed, along with several minor signals. It appears likely from the spectroscopic evidence and the significantly enhanced catalytic activity that under these conditions a different isomerization catalyst is formed than with ethyl vinyl ether. In order to exclude that the isomerization observed with ethanol–NaOH is a base-induced process, dihydropyran **2a** was isolated, purified by distillation and then subjected to the reaction conditions (prolonged heating in toluene–ethanol in the presence of 50 mol% of NaOH). At the end of the reaction, no isomerization was observed and **2a** was recovered unchanged.

The observation that ruthenium carbene complexes show activity in transfer hydrogenation–dehydrogenation reactions[4,12] prompted us to investigate secondary rather than primary alcohols as additives. Ruthenium-catalyzed transfer hydrogenation and dehydrogenation reactions are commonly assumed to proceed *via* ruthenium hydrides as catalytically active species. These are generated by substitution of a ruthenium-bound chlorine by an alkoxide, followed by β-hydride elimination.[13] Gratifyingly, addition of isopropanol and a trace amount of solid NaOH to a metathesis reaction induces conversion of the metathesis catalyst to a highly active isomerization catalyst. For instance, conversion of substrates **1a–c** to enol ethers **3a–c** (Table 1 and Scheme 1), which requires 5–7 h using NaH or $NaBH_4$ as additives, can be achieved within 2 h or less using this method.‡

Having established the superior activity of the isopropanol–NaOH additive combination, we focused on some substrates that showed poor or no reactivity in our previous study. **1d** and **1e**, which undergo the isomerization step only with incomplete



Scheme 1 The ring-closing metathesis–isomerization sequence.

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† Electronic supplementary information (ESI) available: representative experimental procedure and analytical data for products **3**. See http://www.rsc.org/suppdata/cc/b4/b400229f/

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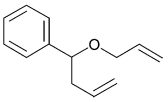
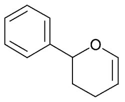
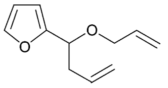
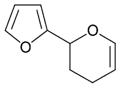
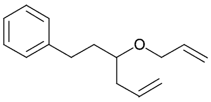
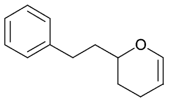
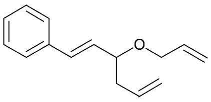
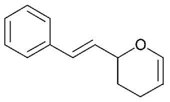
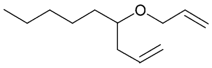
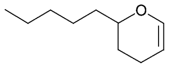
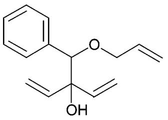
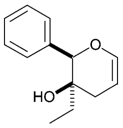
Table 1 Products and yields from the ring-closing metathesis–isomerization sequence[a]

Entry	Starting material (**1**)	Product (**3**)	Yield (%)
1	 **1a**	 **3a**	82
2	 **1b**	 **3b**	75[b]
3	 **1c**	 **3c**	78
4	 **1d**	 **3d**	78[c]
5	 **1e**	 **3e**	70
6	 **1f**	 *rac*-**3f**	65[d]

[a] Refer to Scheme 1. All reactions complete within 2 h, unless otherwise stated. Reagents and conditions: [$Cl_2(PCy_3)_2Ru{=}CHPh$] (5 mol%), toluene (20 °C); then add isopropanol (30% v/v) and NaOH (50 mol%), 110 °C. [b] Complete after 1 h. [c] Complete after 3 h. [d] Complete after 7 h.

conversion if NaH or $NaBH_4$ are used as additives, are smoothly converted to **3d** and **3e**, respectively, under the present conditions. The result obtained for triene **1f** is quite surprising: ring-closing metathesis is a moderately diastereoselective process (dr = 4 : 1)[14] and proceeds in good yields. Attempted isomerization using either NaH or $NaBH_4$ as additives failed completely. With isopropanol–NaOH, the isomerization occurs; however, the exocyclic double bond is selectively hydrogenated. Transfer hydrogenation of alkenes by alcohols is comparatively rare[15] and the factors leading to the preferred hydrogenation of one double bond in **1f** are currently under investigation. To date, we have not been able to identify the actual isomerization catalyst. After completion of the isomerization step, the ^{31}P-NMR spectrum shows a major signal at 51.7 ppm, along with two minor signals at 10.6 and 78.8 ppm. Thus, it appears likely that a different isomerization catalyst is formed if isopropanol rather than ethanol is added to the reaction mixture. Details of the mechanism and the extension of the methodology to other substrates and its application to target molecule synthesis are currently under investigation in our laboratory.

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Notes and references

‡ Representative procedure: to **1a** (354 mg, 1.9 mmol) dissolved in dry toluene (8 mL) was added $Cl_2(PCy_3)_2Ru{=}CHPh$ (78 mg, 5 mol%). The solution was stirred at 20 °C until the starting material was completely consumed (TLC). 2-Propanol (2 mL) and solid NaOH (40 mg, 1.0 mmol) were added. The mixture was heated to reflux until the primarily formed **2a** was completely consumed (TLC). Aqueous work-up followed by flash chromatography gives **1a** (250 mg, 82%).

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